I. General Information

CAS Number: 110-12-3
Name: 2-Hexanone, 5-methyl-
5-Methylhexane-2-one
5-Methyl-2-hexanone
2-Methyl-5-hexanone
3-Methylbutyl methyl ketone
Isoamyl methyl ketone
Isopentyl methyl ketone
Methyl iso-amyl ketone
Methyl isoamyl ketone
Methyl isopentyl ketone
MIAK

II. Physical-Chemical Data

A. Melting Point

Test Substance	
Test substance:	MIAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Melting point value:	-73.9 °C
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 2885
References	Lewis, R.J., Sr. (Ed.). Hawley's Condensed Chemical Dictionary. 12th ed. New York, NY: Van Nostrand Rheinhold Co., 1993.
Other	Last revision date: 19990921

B. Boiling Point

Test Substance	
Test substance:	MIAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Boiling point value:	144 °C
Pressure:	Unknown
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 2885
References	Lide, D.R. (Ed.). CRC Handbook of Chemistry and Physics. 76th ed. Boca Raton, FL: CRC Press Inc., 1995-1996.
Other	Last revision date: 19990921

C. Vapor Pressure

Test Substance	
Test substance:	MIAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Vapor pressure value:	5.77 mmHg
Temperature:	25 ^{o}C
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 2885
References	Alarie, Y. *et al*., Toxicol. Appl. Pharmacol. 134: 92-99, 1995.
Other	Last revision date: 19990921

D. Partition Coefficient

Test Substance	
Test substance:	MIAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Log K_{OW}:	1.88
Temperature:	Unknown
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	Hansch, C., Leo, A.J., and Hoekman, D. Exploring QSAR – Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society, 1995.
Other	Last revision date: 19990921

E. Water Solubility

Test Substance	
Test substance:	MIAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Value:	5,400 mg/L
Temperature:	20^{o} C
Description:	Slight (1-10 g/L)
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 2885
References	Union Carbide Corporation; Ketones. Booklet No. F-41971 pp.21, 1968.
Other	Last revision date: 19990921

III. Environmental Fate Endpoints

A. Photodegradation

Test Substance	
Test substance:	MIAK
Remarks:	
Method	
Method:	Estimation
Test type:	Atmospheric oxidation
Remarks:	
Results	
Temperature:	25 ^{o}C
Hydroxyl radicals reaction	
OH Rate constant:	8.1648 x 10^{-12} cm^3/molecule-sec
Half-life	1.31 Days (12-hr day; $1.5x10^6$ OH/cm^3)
Ozone reaction:	No ozone reaction estimation
Remarks:	
Conclusions	Material is oxidized by atmospheric hydroxyl radicals at a moderate rate.
Data Quality	
Remarks:	
References	AopWin v1.88; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.1, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

B. Stability in Water

Reactivity of Selected Ketones With Water

This report has been prepared Dr. Paul Worsham of Eastman Chemical to document the known chemistry relevant to the stability of selected ketones in aqueous solution. The specific ketones addressed in this document are methyl propyl ketone (MPK; CAS# 107879), methyl isopropyl ketone (MIPK; CAS# 563804), methyl isoamyl ketone (MIAK; CAS# 110123), and methyl n-amyl ketone (MAK; CAS#110430).

Of particular concern in the evaluation of the stability of organic compounds in aqueous solution is the potential for hydrolysis. Hydrolysis is the reaction between water and an organic substrate resulting in the cleavage of existing chemical bonds and subsequent or simultaneous formation of new chemical bonds to form a different chemical compound. Typically, hydrolysis reactions involve incorporation of a water molecule into the structure of the reaction products. For organic substances that participate in hydrolysis reactions, various kinetic methods can be used to monitor the changes in concentration of reactants and determine the rate of transformation of the original substrate into reaction products. OECD Guideline 111 describes one such procedure for measuring the hydrolysis rate of water-soluble substrates as a function of pH. Substrates that exhibit high rates of hydrolysis are considered unstable in an aqueous environment.

Ketones as a class, and specifically the ketones identified above, do not participate in hydrolysis reactions. These ketones do not possess labile leaving groups that can be displaced by the nucleophilic attack of a water molecule, as is required in the mechanism of many hydrolysis reactions. Thus, it would not be meaningful to attempt to measure a hydrolysis rate using a protocol such as OECD Guideline 111.

Certain ketones may add water to form a hydrate under aqueous conditions, especially in the presence of mild acid; but, this addition is an equilibrium reaction that is reversible upon a change in water concentration, and the reaction ultimately leads to no permanent change in the structure of the ketone substrate.[1,2]

A significant property of most ketones is that the hydrogen atoms on the carbons next to the carbonyl group are relatively acidic when compared to hydrogen atoms in typical hydrocarbons. Under strongly basic conditions these hydrogen atoms may be abstracted to form an enolate anion. This property allows ketones, especially methyl ketones such as the four ketones above, to participate in condensation reactions with other ketones and aldehydes. This reaction is called an aldol reaction and generates a higher molecular weight ketone having a hydroxyl group at the site of attack by the enolate anion. This type of condensation reaction is favored by high substrate concentrations and high pH (greater than 1 wt% NaOH). It is conceivable that some alkyl ketones, especially methyl ketones, could participate in aldol reactions in dilute aqueous solution at pH of 9 or higher. But, these reactions would be expected to be slow at ambient temperature, and the equilibrium for condensation of two ketones is unfavorable for aldol product formation[3]. Also, formation of the aldol product is reversible unless dehydration of the aldol occurs. Dehydration of an aldol intermediate in aqueous solution at ambient temperature also would be very slow.

Based on the properties of ketones described above one must conclude that MPK, MIPK, MIAK, and MAK are not subject to hydrolysis, but may participate in other transformations that convert the ketone to higher molecular weight compounds. These reactions would be expected to be very slow at mild temperatures and moderate pH. Therefore, it is my conclusion that MPK, MIPK, MIAK, and MAK should be considered stable in aqueous solution at temperatures and pH levels relevant to environmental and human exposure.

References:

(1) Bell and Clunie, *Trans. Faraday Soc.*, **48,** 439, (1952).
(2) Cohn and Urey, *J. Am. Chem. Soc.*, **60**, 679 (1938).
(3) March, J., ed. "Advanced Organic Chemistry", 3rd edition, p. 831, John Wiley & Sons, New York, 1985.

C. Biodegradation

Test Substance	
Test substance:	MIAK
Remarks:	Purity was 99.3%
Method	
Method:	OECD TG-301D
Test type:	Ready Biodegradability by the Closed Bottle Method
GLP:	Yes
Year:	2001
Contact time:	28-Days
Inoculum:	Activated sludge collected from Wareham, MA wastewater treatment plant
Remarks:	Benzoic acid at 10 mg/ml was used as a reference control. MIAK was assessed at a nominal concentration of 2.5 mg/L. Test vessels of 300ml BOD bottles were prepared per treatment (reference, test substance and inoculum blank), two each for Day 0 and three per sampling interval (Days 7, 14, 21, and 28). After the bottles were filled they were closed and wrapped in tin foil.
Results	
Degradation % at test end:	67% (>60% by Day 14)
Classification:	Readily biodegradable
Remarks:	Benzoic acid reference was degraded 72%. The temperature of the environment ranged from 20-22 ^{o}C. Dissolved oxygen concentrations in the control blank ranged from 8.7 mg/L on Day 0 to 7.1 mg/L on Day 28. The protocol stated that oxygen depletion in the controls should not exceed a loss of 1.5 mg/L before Day 28; however, the loss was 1.6 mg/L. This protocol deviation was viewed as minor and does not affect the overall conclusion as it occurred well after Day 14 when the material had already met the ready biodegradable pass level of >60%.
Conclusions	Material is considered readily biodegradable under the conditions of this test.
Data Quality	
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Methyl Isoamyl Ketone (MIAK) - Ready Biodegradability by the Closed Bottle Method; Springborn Laboratories, Inc Wareham, MA Study No. 1852.6173.
Other	

D. Transport between Environmental Compartments (Fugacity)

Test Substance	
Test substance:	MIAK
Remarks:	
Method	
Test type:	Estimation
Model used:	Level III Fugacity Model; EPIWIN: EQC from Syracuse Research Corporation
Remarks:	
Results	
Model data and results:	Concentration (%)
Estimated distribution and media concentration (levels II/III):	Air 5.68 Water 41.6 Soil 52.7 Sediment 0.112 Physical chemical values utilized in this model were default values obtained from the EPIWIN program.
Remarks:	
Data Quality	
Remarks:	
References	Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.1, Syracuse Research Corporation, Syracuse, New York 13210. The Level III model incorporated into EPIWIN is a Syracuse Research Corporation adaptation of the methodology described by Mackay *et al.* 1996; *Environ. Toxicol. Chem.* **15(9)**, 1618-1626 and *Environ. Toxicol. Chem.* **15(9)**, 1627-1637.
Other	

IV. Ecotoxicity

A. Acute Toxicity to Fish

Test Substance	
Test substance:	MIAK
Remarks:	Unknown
Method	
Method:	Other
Test type:	Static
GLP:	No
Year:	1978
Species/strain:	Fathead minnow (*Pimephales promelas*)
Analytical monitoring:	Yes; Exposure solutions, temperature, pH, dissolved oxygen
Exposure period:	96-Hour
Remarks:	Water was filter-treated lake water with residual chlorine chemically removed. 10 fish per concentration level were used. Exposure solutions were submitted for temperature, dissolved oxygen, and pH concentration determinations at 0, 24, 48, 72, and 96 hrs. Observations for stress and mortality were conducted at 0, 6, 24, 48, 72, and 96 hours.
Results	
Nominal concentration:	100 ul/L
Endpoint value:	LC_{50} >100 ul/L; NOEC > 100 ul/L
Biological observations:	No behavioral abnormalities were noted.
Statistical methods:	NA; no effects were noted at this concentration
Remarks:	Exposure temperature was 19 ^{o}C, pH ranged from 7.4 to 7.9, and dissolved oxygen ranged from 4.8 to 8.7 mg/L.
Conclusions	The LC_{50} value indicates that the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Study lacked some basic information as well as data indicating test material purity and analytical conformation of test concentrations.
References	An Acute Aquatic Effects Test with the Fathead Minnow (*Pimephales promelas*); Environmental Sciences Section, Health and Environment Laboratories, at Eastman Kodak Company, Rochester, NY; HAEL No. 78-0260.
Other	

B. Acute Toxicity to Aquatic Invertebrates

Test Substance	
Test substance:	MIAK
Remarks:	Purity was not available
Method	
Method:	Other
Test type:	Acute immobilization, Static
GLP:	No
Year:	1978
Species/strain:	Daphnid/*Daphnia magna*
Analytical monitoring:	Yes; Exposure solutions, temperature, pH, dissolved oxygen
Exposure period:	96-Hour; static exposure
Remarks:	Water was filter-treated lake water with residual chlorine chemically removed. 10 Daphnids per dose level were used. Exposure solutions were submitted for temperature, dissolved oxygen, and pH concentration determinations at 0, 24, 48, 72, and 96 hrs. Observations for stress and mobility were conducted at 0, 6, 24, 48, 72, and 96 hours.
Results	
Nominal concentration:	100 ul/L
Endpoint value:	EC_{50} (96-hr) > 100 ul/L; NOEC > 100 ul/L
Biological observations:	The *Daphnia* exhibited behavior comparable to controls at all test concentrations.
Statistical methods:	NA; no effects were noted at this concentration
Remarks:	Exposure temperature remained at 19 ^{o}C through out the test, pH was 7.4–7.9, and dissolved oxygen was 4.8-8.7 mg/L.
Conclusions	The LC_{50} value indicates that the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Study lacked some basic information as well as data indicating test material purity and analytical conformation of test concentrations.
References	An Acute Aquatic Effects Test with the Daphnid (*Daphnia magna*); Environmental Sciences Section, Health and Environment Laboratories, at Eastman Kodak Company, Rochester, NY; HAEL No. 78-0260, June 13, 2000
Other	

C. Toxicity to Aquatic Plants

Test Substance	
Test substance:	MIAK
Remarks:	
Method	
Method:	Estimation
Test type:	96-hour Green Algae EC_{50}
Remarks:	ECOSAR class: neutral organics
Results	
EC_{50}:	72.414 mg/L
Remarks:	The 72 hr EC_{50} for reduction of growth and biomass for a structural isomer, methyl amyl ketone (MAK), was 75.5 mg/L and 98.2 mg/L, respectively. The EC_{50} value for this isomer using ECOSAR modeling was 59 mg/L.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	The estimation values derived from the ECOSAR modeling program for both MIAK and MAK, and the actual data from MAK are all quite close.
References	ECOSAR; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.1, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99.8%
Method	
Method:	OECD: TG-201
Test type:	Growth inhibition of algae
GLP:	Yes
Year:	1998
Species/strain:	*Selenastrum capricornutum*
Endpoint basis:	Cell concentrations (biomass) and growth rate
Exposure period:	72-hours
Analytical procedures:	Temperature, light intensity, rpm, and test substance concentration were assessed at the 0, 24, 48, and 72 hours. The pH was assessed at time 0 and after 72 hours.
Remarks:	
Results	
Nominal concentration:	12.5, 25, 50, 100, and 200 mg/L
Measured concentration:	6.2, 11.9, 22.1, 42.7, 86.3 mg/L (geometric mean)
Endpoint value:	The estimated E_bC_{50} (0-72 hr) was 75.5 mg/L; the E_rC_{50} (0-72 hr) was 98.2 mg/L
NOEC:	The 72 hr NOEC was estimated to be 42.7 mg/L
Biological observations:	No deformed cells were noted
Was control response satisfactory:	Yes (culture concentrations increased by a factor of 136-fold)
Statistical methods:	EC_{50} and NOEC values were determined through use of SAS statistical software program AL_ACUTE (Ver. 2.2).
Remarks:	A mean illumination of 741 +/- 1.7 foot-candles was maintained. The mean temperature was 24°C and pH ranged from 7.3 to 7.7. Cultures were oscillated at 100 rpm. The significant loss (up to 82% over the course of the study) in test material was attributed to volatilization. No protocol deviations were noted.
Conclusions	The 72-hour E_bC_{50} and E_rC_{50} values indicate that, based on this study, the test substance would be classified as "harmful to aquatic organisms" according to the European Union's labeling directive and would be classified in a "moderate concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	A Growth Inhibition Test with the Alga, *Selenastrum capricornutum*; Environmental Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study No. EN-512-902185-B; October 13, 1998.
Other	The estimated EC_{50} value using ECOSAR modeling was 59 mg/L. This value is very close to the actual EC_{50} values.

V. Toxicological Data

A. Acute Toxicity

Test Substance	
Test substance:	MIAK
Remarks:	Purity unknown
Method	
Method:	Acute lethality; Other
Test type:	LD_{50} estimate
GLP:	No
Year:	1982
Species/strain:	Rat/unknown
Sex:	Male
Animals/dose:	4
Vehicle:	Undiluted
Route of exposure:	Oral
Remarks:	Animals were administered doses of MIAK at a rate of 1000, 2000, 4000, or 8000 mg/kg. Animals were monitored for 14 days, after which they were terminated, dissected, and examined grossly. The LD50 estimate was determined by the geometric mean of the top two does levels.
Results	
Value:	LD_{50} = 5,657 mg/kg
Deaths at each dose:	1,000 and 2,000 mg/kg: No abnormal effects were noted.
Remarks:	4,000 mg/kg: Clinical signs seen included weakness, ataxia, tremors, and prostration. All recovered and survived to the end of the study. 8,000 mg/kg: All died within one day of dosing with clinical signs consisting of weakness, ataxia, tremors, and prostration.
Conclusions	Material is considered practically non-toxic
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Basic data are given.
References	Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. HAEL No. 78-260, 1982.
Other	

Test Substance	
Test substance:	MIAK
Remarks:	Purity unknown
Method	
Method:	Acute lethality; Other
Test type:	LD_{50} estimate
GLP:	No (Pre-GLP)
Year:	1978
Species/strain:	Rat/unknown
Sex:	Male
Animals/dose:	4
Vehicle:	Undiluted
Route of exposure:	Oral
Remarks:	Initially, four animals each were administered doses of 200, 400, 800, 1,600, or 3,200 mg/kg. An additional two groups of four animals, were administered 1,600 or 3,200 mg/kg several weeks thereafter as it was noted that some of the deaths in the first study may have been a result of aspiration of the test substance. Animals were monitored for 14 days, after which they were terminated, dissected, and examined grossly.
Results	
Value:	LD_{50} >3,200 mg/kg.
Deaths at each dose:	800 mg/kg or less: No deaths. Animals appeared slightly to quite weak on the day of dosing, but normal thereafter.
Remarks:	1,600 mg/kg: One of four died. Animals were weak and transiently ataxic on the day of dosing but appeared normal thereafter. On the repeat study (see remarks above), all animals appeared weak and had roughened coats, but all survived. 3,200 mg/kg: Animals were described as quite weak, and two of four died. On the repeat study, all animals appeared weak and had roughened coats, but all survived.
Conclusions	At most, material is considered slightly toxic
Data Quality	
Reliability:	
Remarks:	Reliable with restrictions Basic data are given.
References	Basic Toxicity of Methyl Isoamyl Ketone, Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. HS&HFL No. 78-260, December 18, 1978.
Other	

Test Substance	
Test substance:	MIAK
Remarks:	Purity unknown
Method	
Method:	Acute lethality; Other
Test type:	LD_{50} estimate
GLP:	No (Pre-GLP)
Year:	1978
Species/strain:	Mouse/unknown
Sex:	Male
Animals/dose:	4
Vehicle:	Undiluted
Route of exposure:	Oral
Remarks:	Initially, four animals each were administered doses of 200, 400, 800, 1,600, or 3,200 mg/kg. Animals were followed for 14 days, after which they were terminated, dissected, and examined grossly.
Results	
Value:	LD_{50} >3,200 mg/kg.
Deaths at each dose:	There were no deaths at any dose.
Remarks:	800 mg/kg and less: Animals appeared slightly weak to normal on the day of dosing and normal thereafter. 1,600 mg/kg: Animals were noted to be excitable with vasodilatation, slight tremors, and weakness on the day of dosing only. 3,200 mg/kg: Animals showed signs of restlessness, vasodilatation, weakness, and prostration on the day of dosing and weakness on Day 3
Conclusions	At most, material is considered slightly toxic
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Basic data are given.
References	Basic Toxicity of Methyl Isoamyl Ketone, Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. HS&HFL No. 78-260, December 18, 1978.
Other	

Test Substance	
Test substance:	MIAK
Remarks:	Purity unknown
Method	
Method:	Acute lethality; Other
Test type:	LC_{50} estimate
GLP:	No (Pre-GLP)
Year:	1978
Species/strain:	Rat/unknown
Sex:	Male
Animals/sex/dose:	4 animals/exposure level
Vehicle:	None
Route of exposure:	Inhalation, whole-body
Remarks:	Rats (181-233 grams) were exposed to MIAK using whole-body chambers for 6 hours at nominal concentrations of 800, 1,600, 3,200, or 6,400 ppm. Actual measured levels were 802, 1,603, 3,207, and 5,878 ppm. After exposure, animals were monitored for clinical observations and weight change for 14-days.
Results	
Value:	
Deaths at each dose:	LC_{50} (6-hr) = 3,813 ppm (17,806 mg/m^3) 800 ppm group: Animals appeared alert during exposure, but appeared a bit sluggish immediately afterwards. Animals gained weight normally. 1,600 ppm: Clinical signs were restricted to sluggish responses after six hours of exposure. All animals gained weight normally throughout the study. 3,200 ppm: Animals displayed eye irritation, unresponsiveness, and impaired gait within two hours. By 4-5 hours of exposure, all rats were narcotized with depressed respiration. One of four animals from this group died just prior to the end of the six-hour exposure period. The remaining three recovered fully following exposure cessation. Weight gain in these animals between Days 0 and 3 was reduced to a total of 3-13 grams, but subsequent weight gain was in the normal range. 6,400 ppm: All animals experienced eye irritation and narcosis, and all animals died within 2.5 hours after initiation of exposure.
Remarks:	
Conclusions	
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Basic data are given
References	Basic Toxicity of Methyl Isoamyl Ketone, Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. HS&HFL No. 78-260, December 18, 1978.
Other	

B. Repeated Dose Toxicity

Test Substance	
Test substance:	MIAK
Remarks:	Purity was 99.1%
Method	
Method:	Other
Test type:	Repeated exposure
GLP:	No
Year:	1981
Species/strain:	Rat/CRL:COBS®CD®(SD)
Route of exposure:	Inhalation
Duration of test:	69 exposures over 96-Days
Exposure levels:	0, 200, 1,000, 2,000 ppm
Sex:	Both
Exposure period:	6 hours/day
Frequency of treatment:	5 days/week
Control group and treatment:	Controls were exposed to room air.
Post-exposure observation period:	None
Remarks:	One hundred twenty rats (60/sex) weighing 217-259 g (M) and 139-199 (F) were randomly assigned to each of the exposure groups (15/sex/dose). Animals were exposed using whole-body chambers. Body weights were recorded once per week and observed for clinical signs before and after exposure each day. At necropsy, complete hematology and clinical chemistry parameters were assessed and a full assortment of tissues was harvested for histological assessment. The liver, kidney, brain, adrenals, testes, ovaries, heart, and spleen were weighed prior to fixation.
Results	
NOEL:	200 ppm (934 mg/m^3)
Actual exposure levels:	212, 1,025, 2,079 ppm

Toxic responses by dose:	2,000 ppm: The body weights of high dose females only were consistently decreased, although never at a statistically significant level. Evidence of irritation was manifested as a porphyrin-like nasal and ocular discharge. During the first 17 days of exposure, moderate lethargy and decreased auditory responses were noted. These effects were described as slight for the remainder of the study. From Day 35 on, gel-like casts were noted beneath the cages. Absolute and relative liver weights were statistically increased in both sexes. Absolute and relative kidney weights were increased in males while relative weights only were elevated in females. This was likely due to the decreased body weights seen in females though. Males only showed a statistically significant increase in platelet count. This effect was deemed to not be of any biological significance though. No other effects were noted in hematology or clinical chemistry. Histopathological changes noted in the liver consisted of minimal to minor hypertrophy (both sexes), minimal to moderate eosinophilic cytoplasmic changes and minor necrosis (males only). In the kidneys, some animals of both sexes showed evidence of minor to moderate tubular regeneration. Males had a possible increase in the severity of hyaline droplet degeneration in the PCT. 1,000 ppm: One male died of unknown causes. Slightly more than half the animals showed evidence of irritation based on a porphyrin-like nasal and ocular discharge. During the first 17 days of exposure, lethargy and decreased auditory responses were noted and described as slight. From Day 35 on, gel-like casts were noted beneath the cages. Absolute and relative liver weights were statistically increased in both sexes. Absolute and relative kidney weights were increased in males only. The same effect on platelets noted at 2000 ppm was observed at this exposure level too. Histological changes in the liver and kidneys of males mirrored what were seen in the 2000-ppm animals but with a decreased rate of incidence and severity (except no PCT degeneration was noted). 200 ppm: No statistically significant effects were noted in any measured parameter.
Statistical methods:	One-way ANOVA followed by Bartlett's Test and Duncan's multiple range test.
Remarks:	
Conclusions	Material was well tolerated with primary target organ effects only occurring at exposure levels that also induced nasal and ocular irritation. The effect in the liver was likely an adaptive response from continual exposure to large doses of test material.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	While this study was not conducted under GLP assurances it nevertheless is a well-documented study that has been published in a peer-reviewed journal.
References	Katz, G.V., Renner Jr, E.R., and Terhaar, C.J. Subchronic Inhalation Toxicity of Methyl Isoamyl Ketone in Rats. *Fund. Appl. Toxicol.* 6, 498-505 (1986).
Other	

Test Substance	
Test substance:	MIAK
Remarks:	Purity was 99.2%
Method	
Method:	Other
Test type:	Repeated exposure
GLP:	No (Pre-GLP)
Year:	1979
Species/strain:	Rat/Charles River CD
Route of exposure:	Oral intubation
Duration of test:	90-days
Dose levels:	0 and 2000 mg/kg
Sex:	8 Males
Frequency of treatment:	A single daily gavage 5 days/week
Control group and treatment:	Yes; Water
Post-exposure observation period:	None
Remarks:	This study involved only a single maximum tolerated dose, and was designed to determine the neurotoxicity and subchronic effects of a series of different ketones against that of n-heptane. Body weight and feed consumption was assessed twice weekly. A full complement of tissues was harvested for histopathology with special emphasis placed on the handling and collection of neural tissues. Several tissues were also weighed. Complete hematology and clinical chemistries were also conducted.
Results	
NOAEL (NOEL):	Not established (Only a single high dose was used)
Toxic responses by dose:	No evidence of neurotoxicity was seen based on an absence of alterations in appearance or behavior, and histological changes in nervous tissue. Feed intake was, in general, slightly depressed throughout the study and was significantly lower during the first week. Body weights were significantly reduced at essentially all time points. There was no effect on the erythron. Effects noted in the clinical chemistry profile included slight, but statistically significant, increases in SGOT, SGPT and urea nitrogen. Urea nitrogen levels were still with in levels seen in historical controls. Absolute and relative increases in liver and adrenal weights were seen. Relative increases were seen in other tissues; however, their significance is negated by a significantly deceased bodyweight. Histological evidence of gastric irritation was manifested by hyperkeratosis, and hyperkeratosis with pseudoepitheliomatous hyperplasia and submucosal thickening and edema. Liver changes consisted of a diffuse hepatocyte hypertrophy, and microfoci of hyperplasia in some rats. The latter effect was characterized by an increase in cytoplasmic and, generally, nuclear size. Three types of nodules were present. The first type was identified on the basis of diffuse increase in cytoplasmic basophilia, the second type contained heavily vacuolated cells, and the third had very large vesicular nuclei with prominent nucleoli. These types of nodules are generally regarded as pre-neoplastic changes. A few animals also exhibited necrosis of individual hepatocytes, a few others had vacuolation of individual hepatocytes. Some animals also had bile duct epithelial hyperplasia. Renal changes included an increased incidence of regenerating tubular epithelium and dilatation with casts, and hyaline droplet formation in the PCT epithelium.

Statistical methods:	One-way ANOVA followed by Bartlett's Test and Duncan's multiple range test.
Remarks:	Other than the finding of a diffuse hepatocyte hypertrophy, the observation of microfoci of hyperplasia was not reproduced following inhalation exposure. Inhalation is the most relevant route by which humans are exposed. Peak blood levels at the highest exposure level in the inhalation study were similar to that following oral intubation.
Conclusions	
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Although this study was completed prior to GLP guidelines, it is still a well-documented study that meets scientific principles.
References	90-Day Repeated Oral Administration of Five Ketones and n-Heptane to Rats. Eastman Kodak Company. Rochester, NY. January 21, 1980.
Other	

C. Genetic Toxicity – Mutation

Test Substance	
Test substance:	MIAK
Remarks:	Purity was >98%
Method	
Method:	EEC Annex V Guideline number B.14 and B.13 (OECD:TG-471-like)
Test type:	*In vitro* mutagenicity
GLP:	Yes
Year:	1999
Species/strain:	*Salmonella typhimurium*/TA98, 100, 1535, 1537, and *Escherichia coli*/WP2*uvr*A(pKM101)
Metabolic activation:	Yes; Aroclor 1254-induced SD rat liver S9
Concentration tested:	Maximum concentration tested was 5000 ug/plate
Remarks:	Positive controls (2-aminoanthracene, 2-nitrofluorene, sodium azide, ICR-191, and 4-nitroquinoline-N-oxide) were run concurrently. DMSO was used as a vehicle and vehicle control.
Results	
Result:	No positive responses were induced in any of the tester strains
Cytotoxic concentration:	>5000 ug/plate (no evidence of cytotoxicity was seen)
Precipitation concentration:	No precipitate was observed at maximum concentration tested.
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical methods:	Mean number of revertants and standard deviations were calculated. Various criteria were established to constitute a valid assay and a positive response was indicated by a 2-3 fold increase in mean revertant number dependent on the bacterial tester strain.
Remarks:	
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented EEC Annex guideline study conducted under GLP assurances.
References	
	Covance Laboratories Inc., Vienna, VA; Study number: 20215-0-409R; March 8, 1999
Other	

D. Genetic Toxicity – Chromosomal Aberrations

Test Substance	
Test substance:	MIAK
Remarks:	Purity was >98%
Method	
Method:	OECD: TG-473
Test type:	*In vitro* mammalian chromosomal aberrations assay
GLP:	Yes
Year:	1999
Species/strain:	Chinese hamster ovary cells (CHO)
Concentrations tested:	Up to 1200 ug/ml (this level meets the 10 mM max. recommended level)
Metabolic Activation:	Yes; Aroclor 1254-induced SD rat liver S9
Remarks:	The positive controls consisted of mitomycin-C and cyclophosphamide. Negative control was the test vehicle dimethylsulfoxide.
Results	
Result:	No significant increases in cells with chromosomal aberrations, polyploidy, or endoreduplication were observed in analyzed cultures.
Cytotoxic concentration:	>1200 ug/ml induced a 14% reduction in confluence
Precipitation concentration:	No precipitate was observed at maximum concentration tested.
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical methods:	Statistical analysis employed a Cochran-Armitage test for linear trends and Fisher's Exact Test to compare the percentage of cells with aberrations.
Remarks:	
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Covance Laboratories Inc., Vienna, VA; Study number: 20215-0-437OECD; April 20, 1999
Other	

E. Developmental Toxicity

Test Substance	
Test substance:	MIAK
Remarks:	Purity was >99%
Method	
Method:	OECD:TG-421
GLP:	Yes
Year:	2001
Species/strain:	Rats/Sprague-Dawley
Sex:	Male and Female (12/exposure level)
Route of exposure:	Inhalation, whole-body
Exposure levels:	0, 1, 2.5, and 5 mg/L
Actual exposure levels:	0.965 ± 0.0724, 2.32 ± 0.137, and 4.72 ± 0.283 mg/L
Exposure period:	6 hrs/day
Frequency of treatment:	7 days/week
Control group and treatment:	Controls were exposed to filtered room air and housed similarly
Duration of test:	Males were exposed for 51 days while females were exposed for 35 to 41 days (through Day 19 of gestation)
Remarks:	The study design also included an analysis of epididymal spermatozoan numbers and motility, and testicular spermatid head counts.
Results	
Maternal toxicity NOAEL:	5 mg/L
Repro./Develop. toxicity NOAEL:	5 mg/L
Parental toxic responses:	All adult animals survived to study termination and there were no test substance-related changes in mean terminal body weight. For the 5 mg/L male group, the mean body weight gain and mean food utilization were higher (p ? 0.05) on Day 35 when compared with the control group. Otherwise, there were no other differences in mean body weight, body weight gain, food consumption, or food utilization among the groups throughout the study. Except for minimal reductions in activity level observed in the 5 mg/L group during each exposure, no other test substance-related clinical abnormalities were noted. Mean sperm motility and mean epididymal spermatozoan and testicular spermatid counts were comparable among the groups. No test substance-related gross pathology was observed for adult animals from any group. No exposure-related changes were observed during histological examination of the reproductive organs of any of the test substance-exposed animals.
Fetal toxic responses dose:	Although trend analyses indicated reductions in the total number of pups per litter and in the number of live pups per litter. The Kruskal-Wallis H-test indicated that the total number of pups per litter and the number of live pups per litter were comparable among the groups. Abnormalities were observed for occasional pups from the 5.0, 2.5, and 0.0 mg/L groups. These abnormalities included the pups appearing small, having no milk in their stomachs, and having bruises under the skin. Additionally, pups were occasionally missing (presumably cannibalized) or found dead. Since the clinical abnormalities were observed for comparable numbers of pups from the control and treated groups and since the number of dead pups was not statistically different among the groups, these findings were not considered to be test substance-related.

Statistical Methods:	Homogeneity of data was evaluated using Bartlett's test (p ? 0.01), one-way analysis of variance (ANOVA) (p ? 0.05), and Dunnett's t-test (p ? 0.05) to indicate statistical significance. When the variances of the means were not considered equal by the Bartlett's test (p ? 0.01), the data were evaluated using a Kruskal-Wallis H-test (p ? 0.05) followed by Mann-Whitney U-test (p ? 0.05). The reproductive performance of the dams and the fertility and fecundity indices were evaluated in contingency tables, using a Chi-square test (p ? 0.05). The total number of pups per litter (live and dead) and the total number of live pups per litter were evaluated using a linear regression model (p ? 0.05).
Remarks:	
Conclusions	Test material did not induce reproductive or developmental toxicity under the conditions of this assay at exposure levels up to 5 mg/L.
Data Quality	
Reliability:	Reliable without restriction
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Reproduction/Developmental Toxicity Screening Test in the Rat. Toxicological Sciences Laboratory; Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study Number HAEL 2000-0208; Laboratory Project ID 2000208I1, March 12, 2001.
Other	

F. Toxicity to Reproduction

See robust summary E above which was a combined developmental/reproductive toxicity screening assessment.